▶ Case 1

A 45-year-old man comes to a community health clinic for his annual physical. He has no major complaints other than his chronic arthritis, which is worsening and is affecting his lower back, hips, and knees. On physical examination, the patient's sclerae are noted to be brownish-blue, and his ear cartilage is similarly discolored. An x-ray of the spine reveals disc degeneration and dense calcification that is most prominent in the lumbar region. Upon voiding for urinalysis, the man's urine is a normal color; however, after standing, the urine turns dark.

What is the most likely diagnosis?	Alkaptonuria (ochronosis).
What is the biochemical defect in this condition?	This disease is characterized by the absence of **homogentisate oxidase,** an enzyme of tyrosine metabolism that catalyzes the conversion of homogentisate to maleylacetoacetate (see Figure 2-1 below). The accumulation of homogentisate in cartilage leads to arthritis as well as to the discoloration of sclerae and other areas of the body.
From which essential amino acid is the accumulated metabolite involved in this defect derived?	Homogentisate is derived from phenylalanine. The defective enzyme is necessary for the metabolism of this amino acid, which is both glucogenic and ketogenic. Homogentisate is normally metabolized to acetoacetate (a ketone) and fumarate (part of the tricarboxylic acid cycle).
Given this patient's extent of joint disease, how might his mental functioning be affected?	Alkaptonuria has no effect on cognitive functioning. Aside from its effects on joints and discoloration of sclerae and skin, the disease is benign.
What is the most appropriate treatment for this condition?	There are no known ways to prevent the buildup of homogentisate. Dietary restriction of tyrosine and phenylalanine will reduce the production of homogentisate, but there has been no demonstrated benefit to this approach. Treating the symptoms of the patient's arthritis is the only recommended therapy in this case.

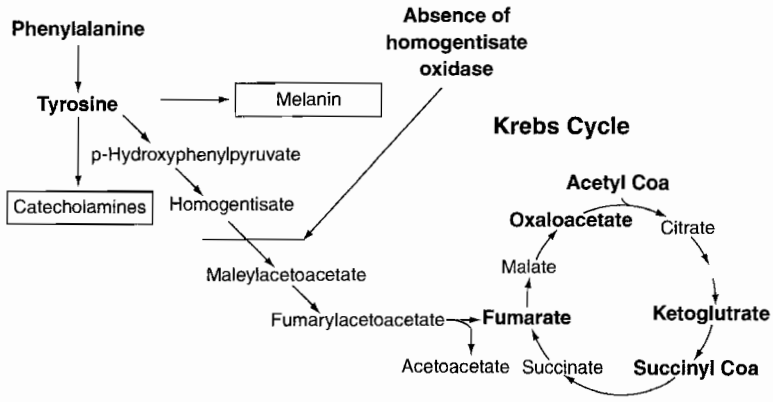

FIGURE 2-1. Flow chart showing conversion of homogentisate to maleylacetoacetate in phenylalanine metabolism.

▶ Case 2

A 37-year-old chemist with a 20-year history of bipolar disorder is rushed to the emergency department by his wife, who found him lying unconscious in the living room of their home. The man's skin is bright red, and he is breathing rapidly. Upon presentation, his breath smells like bitter almonds.

What is the most likely diagnosis?	This man has ingested cyanide (the "bitter almond" breath is pathognomonic).
What biochemical process is disrupted in this condition?	Cyanide is a direct inhibitor of one step in the electron transport chain (see Figure 2-2 below). Cyanide inhibits cytochrome oxidase (CoQ).
Does this patient have a greater-than-normal or lower-than-normal proton concentration in the intermembrane space of his mitochondria?	The man will have a lower proton concentration. The electron transport chain fuels the transport of protons from the mitochondrial matrix to the intermembrane space. Because this patient has ingested cyanide and has thus inhibited this process, his proton gradient is weakened, and therefore he will have a smaller concentration of protons in the intermembrane spaces of his mitochondria.
What is the most appropriate treatment for this condition?	Amyl nitrite. Amyl nitrate oxidizes hemoglobin to methemoglobin. This is normally undesirable because this form of hemoglobin binds oxygen less avidly. However, methemoglobin strongly binds cyanide, preventing it from further disrupting electron transport.
What other substances inhibit the electron transport chain?	Amytal, rotenone, antimycin A, azide, and **carbon monoxide** also inhibit the electron transport chain.
What additional substances disrupt oxidative phosphorylation?	▪ ATPase inhibitors such as oligomycin can directly inhibit the mitochondrial ATPase. Although the proton gradient forms, ATP is not produced. As a result, electron transport ceases. ▪ Uncoupling agents such as 2,4-dinitrophenol (2,4-DNP) increase the permeability of the inner mitochondrial membrane, thereby disrupting the formation of a proton gradient. In this case, electron transport is not disrupted.

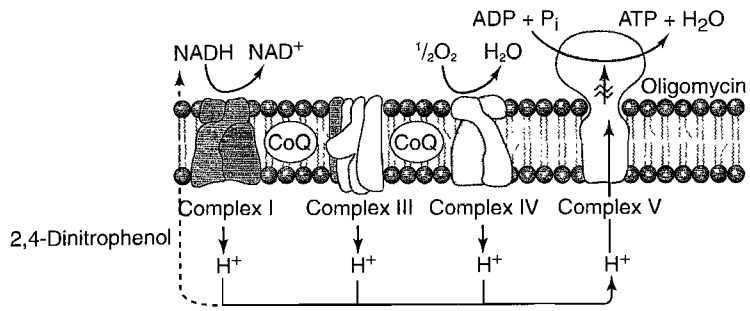

FIGURE 2-2. Cyanide inhibition of oxidative phosphorylation in the electron transport chain. (Reproduced, with permission, from Bhushan V, Le T, et al. *First Aid for the USMLE Step 1: 2006*. New York: McGraw-Hill, 2006: 91.)

▶ Case 3

A 6-year-old boy is followed by his pediatrician for delayed language acquisition and behavioral problems at school. His mother reports a normal pregnancy with adequate prenatal care and adds that she did not use drugs or alcohol during the pregnancy. Genetic analysis reveals a normal 46,XY karyotype but an abnormal-appearing X chromosome. Polymerase chain reaction (PCR) analysis reveals an abnormal region on the X chromosome with 200 CGG trinucleotide repeats.

What is the most likely diagnosis?

This boy has fragile X syndrome, in which methylation of DNA sequences in the promoter area (where the expanded CGG triplets reside) causes silencing of the *FMR1* gene and complete loss of FMR1 protein. The FMR1 protein is involved in mRNA stabilization and transport.

What is PCR?

PCR is a laboratory method used to amplify copies of genes to facilitate detection. First, the patient's DNA is denatured by heat to promote strand separation. During cooling, primers specific for the target gene (in this case the *FMR1* gene) anneal to the patient's DNA and are elongated using a specialized DNA polymerase. The number of copies of the gene is thus doubled. Cycles of heating, annealing, and elongation are then repeated using a thermocycler to produce a logarithmic increase in copies of the target gene.

What is the inheritance pattern of this condition?

Fragile X syndrome is an X-linked genetic disorder. The hallmark of X-linked disorders is the absence of father-to-son disease transmission. X-linked recessive disorders are much more common in males than in females, as females would need two abnormal copies of the gene to show the disease phenotype. In X-linked dominant disorders, males and females are equally affected. Fragile X syndrome is unique in that it is not fully penetrant, and many families show a maternal transmission pattern.

What are other trinucleotide repeat disorders, and why are they associated with "premutations"?

In addition to fragile X, other disorders with a triplet gene (typically CAG) mutation are Huntington's disease, several types of spinocerebellar ataxia, Friedreich's ataxia, and myotonic dystrophy. Typically, higher numbers of trinucleotide repeats result in more severe and earlier onset of the phenotypic expression of disease. Patients with an intermediate number of repeats are said to have a **premutation** because while they themselves are clinically normal, their children are at risk of further increasing the number of repeats and thus expressing clinical disease.

What are the major preventable causes of mental retardation?

In utero infections, maternal drug or alcohol use, and nutritional deficiencies are preventable causes of mental retardation in the fetus.

▶ Case 4

A 5-month-old girl is brought to the pediatrician by her parents because she has been very sleepy lately and has been vomiting and sweating profusely at night. The infant's mother remarks their daughter was doing fine during the first months of her life, but began showing these changes shortly after she began weaning from breast milk. Laboratory testing reveals a serum glucose level of 30 mg/dL, and urinalysis is positive for reducing sugar but negative for glucose.

■ **What is the most likely diagnosis?**	Fructose intolerance.
■ **What intermediate is elevated within the liver cells in this condition?**	Fructose-1-phosphate.
■ **What enzyme is deficient in this condition?**	Aldolase B.
■ **How does this condition cause hypoglycemia?**	Aldolase B splits fructose-1-phosphate into glyceraldehyde and dihydroxyacetone phosphate (DAP) (see Figure 2-3 below). Its absence leads to an accumulation of fructose-1-phosphate in liver cells. The lack of available phosphate inhibits glycogenolysis and gluconeogenesis.
■ **What is the most appropriate treatment for this condition?**	The condition is treated through the removal of sucrose, fructose, and sorbitol from the diet.

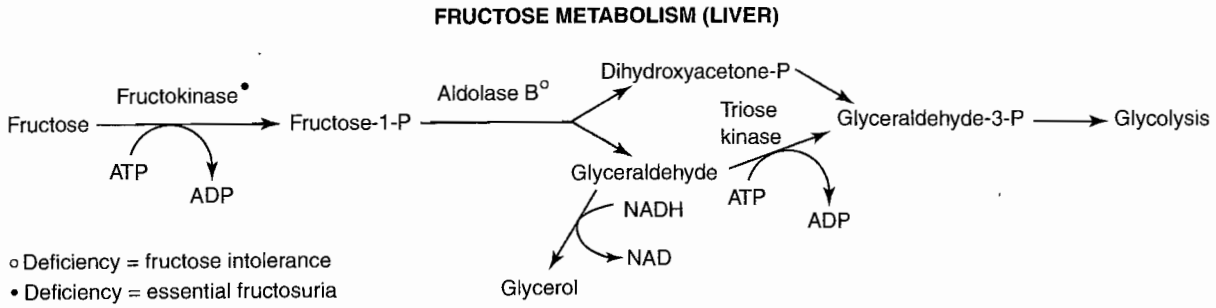

FIGURE 2-3. Aldolase B splitting fructose-1-P into glyceraldehydes and DAP. (Reproduced, with permission, from Bhushan V, Le T, et al. *First Aid for the USMLE Step 1: 2006.* New York: McGraw-Hill, 2006: 93.)

▶ Case 5

A 12-year-old mentally retarded boy is brought into a health clinic in Peru. His parents have noted that he seems to have difficulty with his vision. Physical examination reveals bilateral dislocated lenses and a marfanoid body habitus. Laboratory studies show increased levels of serum methionine and serum homocysteine.

What is the most likely diagnosis?	Homocystinuria.
What is the biochemical defect in this condition?	The most common form of inherited homocystinuria results from reduced activity of **cystathionine synthase,** an enzyme that converts homocysteine to cystathionine (see Figure 2-4 below).
What vitamin supplementation would be appropriate in this condition?	**Vitamin B_6** is a necessary cofactor in cystathionine synthase. **Vitamin B_6** supplementation has been successful in many patients with this enzyme deficiency.
For which conditions is this patient at greatly increased risk?	▪ **Cardiovascular disease:** Elevated plasma homocysteine leads to an increased risk of coronary artery disease, stroke, and peripheral artery disease. ▪ **Osteoporosis:** Homocysteine inhibits collagen cross-linking and over time can cause osteoporosis.
What enzyme deficiency is most likely to be found in a patient with increased serum homocysteine but decreased serum methionine?	This could be caused by a deficiency of methionine synthase. This enzyme catalyzes the conversion of homocysteine to methionine. Like patients with cystathionine synthase deficiency, these patients often have central nervous system dysfunction and vascular disease.

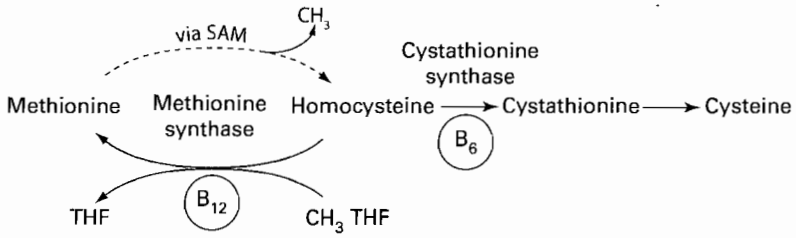

FIGURE 2-4. Homocystinuria. (Reproduced, with permission, from Bhushan V, Le T, et al. *First Aid for the USMLE Step 1: 2006.* New York: McGraw-Hill, 2006: 96.)

▶ Case 6

A 1-year-old boy is brought to the pediatrician because his parents have recently noted a number of abnormalities. Although the child was normal at birth, he does not interact with others as his older sister did at the same age. The parents also note that the child has an abnormally large tongue and coarse facial features. Physical examination reveals multisystem abnormalities. Funduscopic examination shows corneal clouding, and cardiac examination is significant for a 3/5 systolic ejection murmur. Additionally, the baby's liver seems to be enlarged, and his joints are stiff.

What is the most likely diagnosis?	Hurler's syndrome.
What is the pathophysiology of this condition?	This syndrome results from a defect in α-L-iduronidase, an enzyme essential to the degradation of dermatan sulfate and heparin sulfate. This disease is one of the **mucopolysaccharidoses**, a group of hereditary disorders characterized by defects in glycosaminoglycan (GAG) metabolism. In Hurler's syndrome, the GAGs are not appropriately degraded in the lysosomes and are therefore deposited in various tissues. The disease is inherited in an autosomal recessive manner.
What disease has a similar presentation, but is typically milder?	**Hunter's syndrome** is another mucopolysaccharidosis. It is due to a deficiency of iduronate sulfatase and has X-linked inheritance. Unlike Hurler's syndrome, Hunter's syndrome does not present with corneal clouding.
What are the typical findings on electron microscopy?	The lysosomal vesicles will be swollen with partially degraded polysaccharides.
A researcher who wants to use gene therapy to treat this condition successfully clones the defective gene and integrates it into an effective viral vector. After the in vitro experiments fail, the researcher discovers that the cultured cells are secreting the gene product. What went wrong?	α-L-iduronidase is a lysosomal enzyme. These enzymes must be tagged by mannose-6-phosphate in the Golgi apparatus to be targeted to the lysosomes. It is likely that the researcher's gene product is not being tagged properly and has entered the default secretory pathway.

▶ Case 7

A 2-year-old boy is brought to the pediatrician by his mother, who is visibly upset. The mother reports that her son has recently been biting his fingers and scratching his face incessantly. She says he was normal for the first few months of his life but has become increasingly irritable since about 3 months of age. The mother also mentions that her son often has "orange-colored sand" in his diapers. Laboratory studies reveal a serum uric acid level of 55 mg/dL. Urinalysis reveals crystalluria and microscopic hematuria.

What is the most likely diagnosis?	Lesch-Nyhan syndrome.
What is the biochemical defect in this condition?	Lesch-Nyhan syndrome is characterized by a deficiency in hypoxanthine-guanine phosphoribosyltransferase (HGPRT).
What is the function of the deficient enzyme?	HGPRT plays a key role in the purine salvage pathway (see Figure 2-5 below), recycling hypoxanthine and guanine to the purine nucleotide pool. In the absence of this enzyme, these purine bases are degraded into uric acid, resulting in the development of hyperuricemia.
What is the most appropriate treatment for this condition?	Allopurinol inhibits xanthine oxidase, which prevents the formation of uric acid from the more soluble hypoxanthine and xanthine. Doses should be titrated to normalize serum uric acid levels.
What other conditions can be expected if this disease is not treated?	Kidney stones, renal failure, gouty arthritis, and subcutaneous tophi deposits will result if the disorder is left untreated.

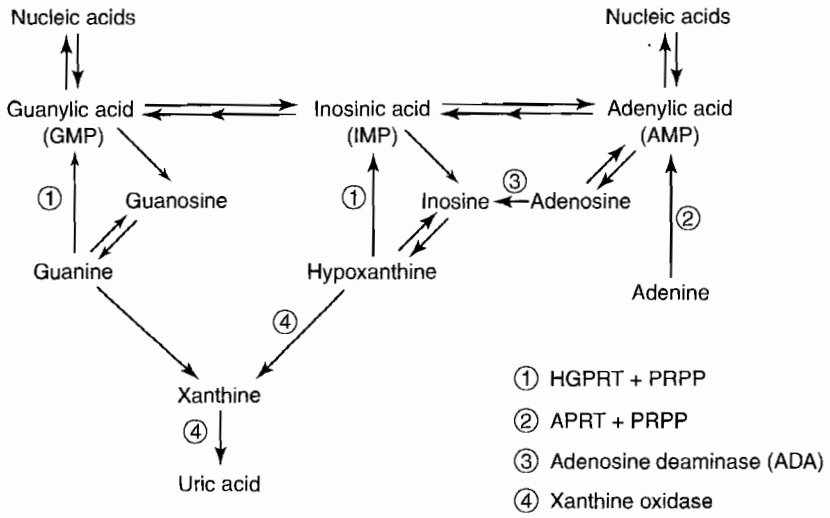

FIGURE 2-5. Purine salvage pathway. (Reproduced, with permission, from Bhushan V, Le T, et al. *First Aid for the USMLE Step 1: 2006*. New York: McGraw-Hill, 2006: 97.)

▶ Case 8

A 19-year-old female college student comes to the university health clinic complaining of muscle aches. She recently began an exercise program in an attempt to lose the 6–8 kg (15 lb) that that she had gained over the past year. After her first day of weight lifting, however, she became extremely sore. Several hours later, her urine was the color of "cherry soda pop." Physical examination is unremarkable. Laboratory tests reveal a serum creatine kinase level of 93,970 IU/L. Urinalysis is negative for blood and positive for myoglobin.

▪ **What is the most likely diagnosis?**	McArdle's disease (type V glycogen storage disease).
▪ **What is the biochemical defect in this condition?**	McArdle's disease is caused by a deficiency of muscle glycogen phosphorylase. Although glycogen formation is not affected, glycogen cannot be broken back down to glucose (glycogenolysis) because the α-1,4-glycosidic bonds cannot be broken in the muscle to release glucose-1-phosphate.
▪ **What are the most likely findings on biopsy of the liver and muscle?**	A liver biopsy will be normal, as the defective enzyme is present only in muscle. Muscle biopsy will show subsarcolemmal and intermyofibrillar accumulation of glycogen.
▪ **After the patient completes an exercise tolerance test, her lactic acid levels do not increase normally. Why?**	Lactic acid is a product of anaerobic glucose metabolism. Failure of lactic acid levels to elevate after exercise is an indication of a defect in the metabolism of glycogen or glucose to lactate. This response can be seen in other disorders of glycogenolysis or glycolysis as well.
▪ **What is the most appropriate treatment for this condition?**	Oral ingestion of sucrose before exercise has been demonstrated to improve exercise tolerance and reduce the risk of myoglobinuria.

▶ Case 9

A 2-year-old boy is brought to a health clinic in Peru because of poor development as well as vomiting, irritability, and a skin rash. The boy's mother also notes that his urine has a strange "mousy" odor. Physical examination reveals the child has an eczema-like rash, is hyperreflexive, and has increased muscle tone. He is surprisingly fair-skinned in comparison to the rest of his family. Laboratory studies reveal a positive Guthrie test and a serum phenylalanine level of 28 mg/dL.

What is the most likely diagnosis?	Phenylketonuria (PKU).
What is the pathophysiology of this condition?	PKU is caused by a defect in the metabolism of **phenylalanine** (see Figure 2-6 below). Normally, this essential amino acid is converted to tyrosine by phenylalanine hydroxylase. However, when phenylalanine hydroxylase activity is reduced or absent, phenylalanine builds up, leading to excess phenyl ketones in the blood and resulting in the symptoms seen in this patient. In patients with PKU, tyrosine cannot be derived from phenylalanine, so it becomes an essential amino acid. PKU is inherited in an autosomal recessive fashion.
What additional physical characteristics are common at presentation?	Other physical findings include failure to thrive, mental retardation, microcephaly, large cheek and upper jaw bones, and widely spaced teeth with poorly developed enamel.
What is the cofactor for the defective enzyme in this disease that, when deficient, can also lead to increased levels of phenylalanine in the blood?	A deficiency in tetrahydrobiopterin can also lead to increased blood levels of phenylalanine.
What is the most appropriate treatment for this condition?	PKU should be treated with decreased dietary phenylalanine (which is contained in NutraSweet) and increased dietary tyrosine. Studies suggest continuation of dietary restrictions throughout life is necessary for optimal outcomes.

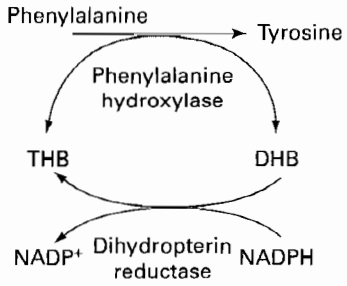

FIGURE 2-6. Metabolism of phenylalanine. (Reproduced, with permission, from Bhushan V, Le T, et al. *First Aid for the USMLE Step 1: 2006.* New York: McGraw-Hill, 2006: 95.)

▶ Case 10

A 6-month-old baby is brought to the pediatrician because she has been feeding poorly and has been lethargic for the past several months. The baby has also started breathing more rapidly than normal and recently had a seizure. Laboratory studies reveal a serum pH of 7.20, an anion gap of 19, elevated levels of pyruvate and alanine, and decreased levels of citrate.

■ **What is the most likely diagnosis?**	Pyruvate dehydrogenase deficiency.
■ **What is the pathophysiology of this condition?**	Pyruvate dehydrogenase converts pyruvate to acetyl-CoA (see Figure 2-7 below). Without it, glucose and amino acids cannot be shunted to the tricarboxylic acid (TCA) cycle to be used for energy. This baby has a lactic acidosis because she is relying heavily on glycolysis for energy.
■ **Why are alanine levels high and citrate levels low in this condition?**	Pyruvate levels are high because much of the excess pyruvate is converted to alanine in a reversible reaction by alanine aminotransferase. Citrate levels are low because pyruvate cannot be converted to acetyl-CoA to replenish the TCA cycle intermediates. Citrate is one such intermediate.
■ **What is the most appropriate treatment for this condition?**	Treatment involves increased intake of ketogenic nutrients (foods with high fat content). These foods will provide energy without necessitating use of the citric acid cycle. Oral citrate is also helpful in replenishing the substrates of the citric acid cycle.
■ **Which are the only purely ketogenic amino acids?**	Leucine and lysine are the only purely ketogenic amino acids.

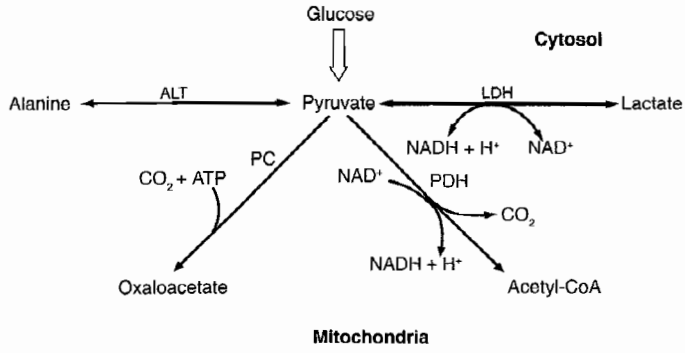

FIGURE 2-7. Pyruvate metabolism. (Reproduced, with permission, from Bhushan V, Le T, et al. *First Aid for the USMLE Step 1: 2006*. New York: McGraw-Hill, 2006: 149.)

▶ Case 11

A 5-month-old girl is brought to her pediatrician by her parents, both of whom are Jewish. Although the baby girl was developing normally for the first 4 months of her life, she can no longer roll over by herself. In addition, while she often smiled at 3 months of age, she no longer does so. Funduscopic examination reveals a "cherry-red" spot on her macula.

What is the most likely diagnosis?	Tay-Sachs disease.
What is the biochemical defect in this condition?	This disease, one of the sphingolipidoses, is caused by a deficiency of **hexosaminidase A.** This enzyme is present within the lysosomes of central nervous system cells and helps degrade a lipid called GM2 ganglioside. GM2 ganglioside accumulation within the neurons leads to progressive neurodegeneration. Children become blind and deaf before paralysis ultimately sets in. Children with Tay-Sachs disease usually die by age 3 years.
How is this gene responsible for this condition inherited?	Tay-Sachs disease is inherited in an autosomal recessive fashion. Fabry's disease is the only one of the sphingolipidoses that is inherited differently; it is X-linked.
What other conditions present with similar findings on physical examination?	**Niemann-Pick disease,** which is caused by a deficiency of sphingomyelinase, also presents with a cherry-red spot in the macula in about 50% of cases. These patients often present with anemia, fever, and neurologic deterioration. The prognosis of Niemann-Pick disease is poor as well, with most patients dying by age 3 years.
Which of the other sphingolipidoses also has a higher prevalence among Ashkenazi Jews?	**Gaucher's disease,** which is caused by a deficiency of β-glucocerebrosidase, also has a much higher incidence in this population.

▶ Case 12

A 36-year-old homeless man presents to a community health clinic complaining of increasing shortness of breath. On questioning, the man admits to an extensive history of alcoholism. A review of systems reveals he has also experienced tingling and burning in his legs for the past several weeks. Physical examination reveals that he is tachycardic (heart rate 122/min), has rales bilaterally, and has bilateral pitting edema. He also has decreased sensation in his feet and is hyporeflexive in his lower extremities. An x-ray of the chest shows an enlarged cardiac silhouette and bilateral pulmonary congestion.

What is the most likely diagnosis?	Vitamin B_1 (thiamine) deficiency.
What clinical manifestations are commonly present in this condition?	This patient has the symptoms of both wet and dry beriberi. Patients with **wet beriberi** present with high-output congestive heart failure and dilated cardiomyopathy. Patients with **dry beriberi** present with peripheral neuropathy consisting of muscular atrophy and diminished sensation and reflexes.
The deficient factor in this condition serves as a cofactor for which enzymes?	Thiamine is part of thiamine pyrophosphate (TPP). This acts as a cofactor for transketolase (an enzyme in the HMP shunt) (see Figure 2-8A below), pyruvate decarboxylase (a component of the pyruvate dehydrogenase complex), and α-ketoglutarate decarboxylase (a component of the α-ketoglutarate dehydrogenase complex) (see Figure 2-8B below).
What other pathologies are commonly seen with this vitamin deficiency?	**Wernicke's encephalopathy** is the central nervous system manifestation of thiamine deficiency. This disease classically consists of nystagmus, ophthalmoplegia, and cerebellar ataxia. When the additional symptoms of confusion/psychosis and confabulation are seen, the disease is known as **Wernicke-Korsakoff syndrome.**
What are the most likely findings on MRI?	Although degenerative changes are often seen in the cerebellum, brain stem, and diencephalon, atrophy of the mammillary bodies is most commonly noted.

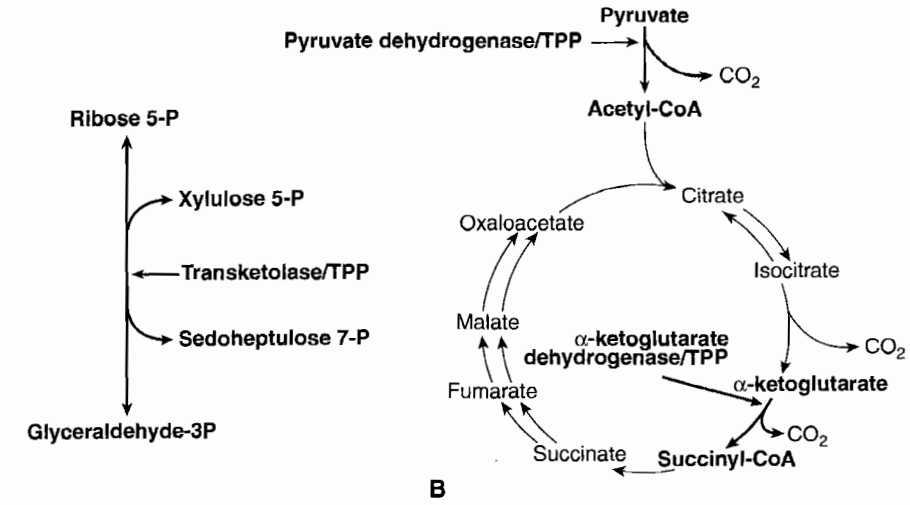

FIGURE 2-8. (A) Thiamine in HMP shunt; (B) Thiamine in TCA cycle.

▶ Case 13

A 6-month-old girl is brought to her pediatrician because of a 5-month history of restlessness, vomiting, and sweating. Her parents brought her in today after she had a seizure. On questioning, the parents note that the infant's symptoms most commonly occur between meals and subside after feeding. On physical examination, the baby is determined to be small for her age with a protuberant abdomen and xanthomas on the buttocks. Ultrasound shows hepatomegaly and bilaterally enlarged kidneys. Relevant laboratory values are as follows:

Serum glucose: 20 mg/dL
Anion gap: 35
Lactic acid: 9 mg/dL

What is the most likely diagnosis?	von Gierke's disease (type I glycogen storage disease).
What is the biochemical defect in this condition?	This is a glycogen storage disease resulting from glucose-6-phosphatase deficiency. While the liver is able to create and store glycogen, it is unable to break it down into glucose, because glucose-6-phosphatase (which catalyzes the final step of this process) is deficient (see Figure 2-9). The result is the absence of the normal buffering capacity provided by glycogen metabolism, resulting in marked fasting hypoglycemia.
What are the most likely findings on liver biopsy?	Glycogen lipid droplets and significant steatosis are most likely to be found on microscopy.
What complications are commonly associated with this condition?	• Gout can develop as a result of hyperuricemia. • Hyperlipidemia—especially hypertriglyceridemia—is also common and can lead to xanthoma formation and pancreatitis. • Platelet dysfunction is common as well and presents as easy bruising and epistaxis. • Over time, patients may develop liver adenomas that occasionally undergo malignant transformation. • Nephropathy often develops from the accumulation of glycogen in the kidney.
What is the most appropriate treatment for this condition?	The most appropriate treatment consists of frequent meals to prevent hypoglycemia. Some patients make cornstarch a central part of their diet because it is absorbed slowly and provides a steady glucose supply. Allopurinol is often used for gout. Liver transplantation is curative.

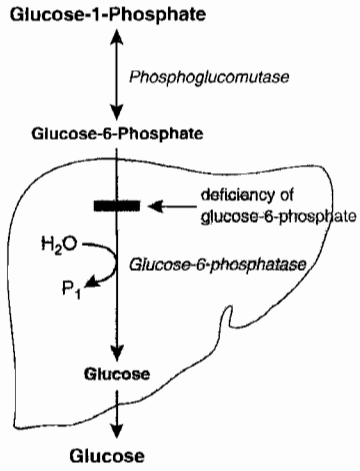

FIGURE 2-9. Glucose-6-phosphatase deficiency.